Association of Maternal Serum C- Reactive Protein Levels
with Severity of Preeclampsia

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Abstract- The aim of this study was to investigate C-reactive protein (CRP) level in preeclampsia (PE) and its association with the severity of the disease. This cross-sectional study included 43 women with mild PE, 43 women with severe PE, and 43 healthy pregnant. They were selected in the third trimester of pregnancy in the Afzalipour Hospital, Kerman, Iran, from March 2006 to March 2007. Mean diastolic pressure and level of proteinuria were used as indicators of the severity of the disease. The results were analyzed by t-test and spearman's rank correlation coefficient. Hemoglobin, aspartate and alanine transaminase, creatinine and urine protein excretion, serum CRP, and alkaline phosphatase were higher in women with PE. There were significant correlations between serum CRP levels and diastolic blood pressure ($r = 0.5$, $P = 0$), urinary protein excretion ($r = 0.5$, $P = 0$), creatinine ($r = 0.2$, $P = 0.003$), spartate transaminase ($r = 0.3$, $P = 0$), alanine transaminase ($r = 0.2$, $P = 0.006$), and Hemoglobin ($r = 0.2$, $P = 0.001$). There were a negative correlation between serum CRP and weight of the new born ($r = -0.09$, $P = 0.01$) and gestational age in the time of delivery ($r = -0.07$, $P = 0$). We showed higher levels of CRP in women with PE. Elevated serum levels of CRP in PE women are, thus, correlated with severity of disease.

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Introduction

Preeclampsia (PE) develops in 4-5% of human pregnancies. It is characterized by an elevated blood pressure and proteinuria and develops after 20 weeks of gestation (1). PE is a complication of pregnancy constituting a major cause of maternal and fetal morbidity and mortality. Several etiologies have been implicated in the development of preeclampsia including abnormal trophoblast invasion of uterine blood vessels and immunological intolerance between fetoplacental and maternal tissues (2).

Endothelial cell dysfunction and inflammation are considered to have a role in the pathophysiology of PE (3,4). A generalized activation of circulating leukocytes, characteristic of inflammation, has been found during PE. Moreover, increased concentrations of CRP and inflammatory cytokines have been reported in PE women (5).

CRP is produced by the liver and the production is stimulated by the inflammatory cytokines interleukin-6 and TNF-alpha. CRP is a sensitive marker of inflammatory activity in the body. CRP level increases during inflammatory response to tissue injury or infection (6).

The aim of this study was to determine serum CRP level in PE, and its association with the severity of the disease and with bioehemica1 and clinical parameters.

Patients and Methods

This cross-sectional study was conducted in Afzalipour an University Hospital, Kerman, Iran, over a 1-year period from March 2006 to March 2007. The study was performed in three groups of women. Group1 consisted of 43 women with mild preeclampsia at the time of admission; group 2 included 43 women with severe preeclampsia, and group 3 consisted of 43 healthy normotensive women in the third trimester of their pregnancy.

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Normal pregnancy was diagnosed on the basis of clinical and biochemical findings.

All groups had gestational ages of 28-40 weeks, not in labor and singleton. Patients with a history of diabetes, renal disease, chronic hypertension, systemic lupus erythematosus, systemic infection and cardiovascular disease were excluded during routine interviews, clinical investigations and laboratory tests.

PE was diagnosed according to the following criteria: a blood pressure higher than 140/90 mm Hg and proteinuria more than 300 mg/24h or protein dipstick $\geq$ 1+ on $\geq$ 2 midstream samples 6 hours apart. Severe PE was classified if diastolic blood pressure increased to at least 110mgHg, Proteinuria > 2000 g/24h or protein dipstick $\geq$ 2+ on $\geq$ 2 midstream samples 6 hours apart, and the presence of headache, visual disturbances, epigastric pain, oliguria (30cc/l), increased bilirubin, elevated serum creatinine levels ($\geq$ 0.9 mg/dl), thrombocytopenia (< 100.000 mm^3), and elevated aspartate and alanine transaminase levels.

Blood samples were drawn on admission in the morning after a 6h fasting and before magnesium sulfate administarion. Serum CRP levels were measured by high CRP sensitivity kits using an immunoturbidimetric method with a detection limit of 0.03 mg/l.

The results were expressed as mean $\pm$ SD and analyzed by an independent samples t-test. The correlation analysis was done by spearman's test.

All statistical analyses were carried out by using a SPSS software, version 13. The level of significance was set at $P < 0.05$.

Results

The demographic and clinical parameters of the groups are summarized in table 1.

Maternal age was not significantly different between the groups ($P > 0.05$, table 1). Mean systolic and diastolic blood pressures were higher in PE groups as compared to healthy women values ($P = 0.001$, Table 1).

Gestational age was significantly different between the groups ($P = 0.0001$, Table 1).

Serum CRP levels in mild and severe PE were markedly higher than those of normal third trimester pregnant women (Table 2).

The hemoglobin levels, platelet count and blood urea nitrogen, creatinine, aspartate transaminase (AST), alanine transaminase (ATT), and Alkaline phosphatase were higher in mild and sever PE (Table 2). Bilirubin levels were found to be similar in three groups.

Table 1. Demographic and clinical parameters of groups

	Healthy group	Mild PE	Sever PE	P-Value
Maternal age	26.31 ± 5.13	27.6 ± 6.14	28.62 ± 5.40	NS
Gestational age	38.63 ± 1.87	36.86 ± 3.45	35.34 ± 3.66	P = 0.0001
Systolic BP (mmHg)	109.17 ± 9.81	137.38 ± 4.96	162.50 ± 14.15	P = 0.001
Diastolic BP(mmHg)	71.90 ± 7.56	88.21 ± 8.17	96.43 ± 1.42	P = 0.001
Birth weight (kg)	3.16 ± 0.53	2.89 ± 0.53	2.64 ± 0.7	P = 0.0001

NS: Non Significant, **BP:** Blood Pressure

Table 2. Biochemical parameters of study groups

	Healthy group (n=43)	Mild preeclampsia (n=43)	Sever preeclampsia (n=43)	P-Value
CRP(mg/l)	3.42 ± 5.48	14.28 ± 11.62	34 ± 25.27	P = 0.003
ALT(u/l)	20.79 ± 5.93	21.26 ± 5.69	37.33 ± 31.39	P = 0.001
AST(u/l)	15.93 ± 6.63	17.88 ± 5.23	38.05 ± 38.77	P = 0.0001
Creatinine (mg/dl)	0.75 ± 0.24	0.79 ± 0.20	0.93 ± 0.25	P = 0.002
Blood urea nitrogen (mg/dl)	22.88 ± 7.54	23.33 ± 7.77	28.50 ± 8.59	P = 0.002
Alkalin phosphatas	253.43 ± 84.50	242.12 ± 113.33	308.48 ± 142.49	P = 0.007
Hemoglobin (mg/dl)	12.59 ± 7 .54	13.47 ± 1.35	15.03 ± 1.35	P = 0.0001
Total Bilirubin (mg/dl)	0.41±0.12	0.4±0.2	0.46±0.20	P=0.19

AST: Aspartate Transaminase, ALT: Alanine Transaminase

In mild to severe PE groups, correlation tests showed a positive correlation between serum CRP levels and systolic blood pressure (r = 0.6, *p* = 0), diastolic blood pressure (r = 0.5, *P* = 0) , creatinine levels (r = 0.2, p = 0.003), blood urea nitrogen (r=0.2, p=0.004), urinary protein excretion (r = 0.5, *P* = 0.00), ALT (r = 0.2, *P* = 0.006), AST (r = 0.3, *P* = 0/001), Hemoglobin level (r = 0.2, *P* = 0.001), and Alkalin phosphatas (r = 0.19, r = 0.003). There was a negative correlation between CRP and birth weight (r = -0.09, *P* = 0.01) and gestational age (r = -0.4, *P* = 0).

Discussion

Preeclampsia is a disease of pregnancy associated with endothelial cell damage. There is increasing evidence that preeclampsia is a systemic inflammatory disease (2).

Studies have shown that markers of endothelial activation or inflammation have an active role in preeclampsia (7).

CRP, a sensitive marker of tissue damage and inflammation, was proposed to play a role in eliciting the inflammatory response characteristics of preeclampsia (2).

In this study, we have clearly shown that serum CRP levels were higher in Preeclampsia woman as composed to healthy pregnant controls. Similarly, there are studies reporting that serum CRP levels increase in preeclamptic woman (1, 2). There are few studies concerning correlation of CRP levels with severity of preeclampsia. Determination of serum CRP levels in the third trimester pregnant women proved of great value in predicting the prognosis of preeclampsia. Proteinuria and blood pressures are used as parameters for severity of PE (8).

We found a positive correlation between serum levels of CRP and diastolic and systolic blood pressure and urinary protein excretion in PE. Endothelial dysfunction of PE has been associated with an exaggerated maternal inflammatory response to pregnancy. It has been hypothesized that placental hypoxia, resulting from utero-placental arterial insufficiency, amplifies the release of inflammatory stimuli into the maternal circulation (9).

In our study, there was a positive correlation between CRP levels and biochemical parameters (ALT, AST, Bun-creatinine, hemoglobin, proteinuria)

Kumru *et al.* (2006) (1) showed a positive correction between serum CRP levels and diastolic blood pressure and urinary protein excertion (1). Another study found a significant correlation between mean arterial pressure and CRP (r = 0.515, *P* = 0.0001) in pregnancies compli-

cated with preeclampsia .In this study, correlation of CRP level with other biochemical and clinical parameters of severe preeclampsia was not evaluated (2).

Erren *et al.* (1999) reported that inflammatory profile was more pronounced when the endothelial damage was more advanced. It is well known that renal dysfunction usually occurs in PE, especially in its severe forms. In cases of renal dysfunction, endothelial dysfunction and increased inflammatory markers such as CRP have been shown (10-12).

The mean gestational age was less in our study for the Preeclamptic women than the healthy (healthy = 38.68, mild = 36.86 severe = 35.34, *P* = 0.0001) and in the preeclamptic groups, there was a statistically significant negative correlation between gestational age and maternal CRP concentration (r = -0.4, *P* = 0)

The higher CRP levels in patients with Preeclampsia delivering earlier in pregnancy could probably be a marker of disease severity and a marker of an excessive inflammatory response in patients with the most severe PE disease delivering prematurely compared with patients with less severe disease who deliver later in pregnancy (6).

Our findings of elevated serum levels of CRP are associated with low birth weight and a negative correlation between serum CRP levels and weight of the newborns in preeclampsia groups. It is well known that PE increases the risks of intrauterine growth restriction and low birth weight (13). Kurmus *et al.* (2006) found a negative correlation between serum CRP and weight and length of the newborns in the PE group in comparison with the control group (1). CRP level, a marker of inflammatory response, is raised in healthy pregnant women compared with non-pregnant women. However, factors such as age, labor, infections and medical disease are associated with raised concentrations of CRP. In this study, all groups were matched for maternal age, none had chronic medical disorders or were in labor (14). However, we found an evidence for presence of inflammation in preeclampsia. CRP levels correlated positively with the severity of disease. We also showed a positive correlation between serum CRP and biochemical and clinical parameters in preeclampsia.

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